REMARKS

Newly introduced claims 31-51 are drawn, as per cancelled claims 1-11 and 20-30, to the ability of exendin and exendin agonists, including analogs and derivatives of exendin, to influence gastric activity in a subject. These amendments are plainly not made for reasons related to patentability, but merely to make the language in each claim consistent with language in other claims. Applicants also note that, as compared to previous independent claim 1, new independent claims 31-34 do not narrow the scope of subject matter included within the scope of originally filed claim 1. Support for the new claims can be found throughout the specification, including, e.g., the originally filed claims, page 1, lines 9-13, page 6, lines 4-10, and page 13, lines 4-6. In accordance with 37 C.F.R. §1.121(b), a marked up version of the paragraph amendment is appended hereto, with additions noted by underline and deletions noted by brackets.

As a preliminary matter, Applicants wish to thank the Examiner for the telephonic interview she so graciously extended on May 25, 2001. In addition to other matters set forth herein, it is Applicants' understanding from that interview that the Examiner ultimately agreed that the claim terms "exendin," "exendin derivative," and "exendin analog" as described in the application do not include GLP-1.

I. REJECTIONS

A. The Rejections Under 35 U.S.C. § 112, ¶ 2, Definiteness

1. The claim term "therapeutically effective amount"

Claims 1-11 and 20-30, now cancelled, stood rejected under 35 U.S.C. §112, ¶ 2, as allegedly indefinite respecting the claim term "therapeutically effective amount." Certain new claims contain the same term. The Examiner contends that this per se lacks a "clear and measurable endpoint." Applicants respectfully traverse.

The phrase "effective amount" in a claim does not automatically mean that the claim is indefinite for failing to particularly point out and distinctly claim the subject matter that Applicants regard as the invention. The test is whether or not one skilled in the art could

determine appropriate amounts based on the disclosure. *See In re Mattison*, 509 F.2d 563, 184 USPQ 484 (CCPA 1975); *accord* MPEP §2173.05(c)(III). The Board of Patent Appeals and Interferences, in *Ex parte Skuballa*, 12 USPQ2d 1570 (BPAI 1989), has additionally held, with respect to pharmaceutical composition claims, that a functional utility must also be specified.

The instant claims satisfy these requirements. Ample clarity and guidance exists in the following specification passage alone to demonstrate this:

> ...Therapeutically effective amounts of an exendin or exendin agonist for use in the control of gastric emptying and in conditions in which gastric emptying is beneficially slowed or regulated are those that decrease post-prandial blood glucose levels, preferably to no more than about 8 or 9 mM or such that blood glucose levels are reduced as desired. In diabetic or glucose intolerant individuals, plasma glucose levels are higher than in normal individuals. In such individuals, beneficial reduction or "smoothing" of post-prandial blood glucose levels, may be obtained. As will be recognized by those in the field, an effective amount of therapeutic agent will vary with many factors including the age and weight of the patient, the patient's physical condition, the blood sugar level or level of inhibition of gastric emptying to be obtained, and other factors.
>
> Such pharmaceutical compositions are useful in causing gastric hypomotility in a subject and may be used as well in other disorders where gastric motility is beneficially reduced.
>
> The effective daily anti-emptying dose of the compounds will typically be in the range of 0.001 or 0.003 to about 5 mg/day, preferably about 0.001 or 0.5 to 2 mg/day and more preferably about 0.001 or 0.01 to 1 mg/day, for a 70 kg patient, administered in a single or divided doses. The exact dose to be administered is determined by the attending clinician and is dependent upon where the particular compound lies within the above quoted range, as well as upon the age, weight and condition of the individual. . . .
>
> The optimal formulation and mode of administration of compounds of the present application to a patient depend on factors known in the art such as the particular disease or disorder, the desired effect, and the type of patient.

Specification, page 28, line 2 to page 29, line 15 (emphasis added). In addition, page 1, lines 9-13, and page 5, lines 15-20, contain specific indications of the use of exendins and exendin agonists for delaying gastric emptying, and specify that such uses are beneficial in the treatment of, e.g., diabetes mellitus, obesity, ingestion of toxins, and diagnostics. Examples 1-3 of the specification, beginning on page 29 of the specification, further demonstrate how such may be accomplished. Specific values are provided, as are numerous utilities.

Accordingly, Applicants respectfully submit that the claim terms "therapeutically effective amount" and "effective amount" are definite within the meaning of 35 U.S.C. §112, ¶ 2 and request that the Examiner reconsider and withdraw this ground of rejection.

2. The claim term "exendin"

The Examiner alleged that claim 1, now cancelled, was indefinite in use of the term "exendin." Applicants respectfully disagreed with this contention and it is understood that the Examiner ultimately agreed with Applicants in the telephonic interview of May 25, 2001. The new claims possess the same term.

The test for definiteness is whether one skilled in the art would understand the bounds of the claim when read in light of the specification. The claims must be read in light of the specification and need only reasonably apprise those skilled in the art of the scope of the invention. *Miles Lab., Inc. v. Shandon, Inc.*, 997 F.2d 870, 875, 27 USPQ2d 1123, 1126 (Fed. Cir. 1993); *Andrew Corp. v. Gabriel Electronics, Inc.*, 847 F.2d 819, 6 USPQ2d 2010 (Fed. Cir. 1988), *cert. denied*, 488 US 927 (1988).

As noted by the Examiner, two exendins, exendin-3 and exendin-4, are clearly disclosed in the application and representative of the exendin genus. These two species possess distinct amino acid sequences and originate from distinct species of lizards. *See, e.g.*, specification, page 1 bridging page 2. The law does not place a restriction on the size of the genus nor require that every exendin in the genus be described or appreciated before securing protection to a claim directed to the genus. The law allows for the future discovery and protection of additional species within a presently claimed genus. *See, e.g., Hormone Research Foundation Inc. v.*

Genentech Inc., 15 USPQ2d 1039, 1048 (Fed. Cir. 1990) ("Merely because purer and more potent forms of the Figure 2 compound might be produced using later-discovered technology does not necessarily mean that the '833 patent specification did not provide sufficient enabling disclosures as of the filing date of the application."

It is both reasonable and readily apparent to one of ordinary skill in the art reading the instant application that the claim term "exendin" embraces at least exendins 3 and 4. Accordingly, Applicants ask that this ground of rejection be reconsidered and withdrawn.

3. The claim terms "exendin analog" and "exendin derivative"

The Examiner alleged that claim 1, now cancelled, was indefinite in the use of the claim terms "exendin analog" and "exendin derivative." In the telephonic interview of May 25, 2001, the Examiner agreed that these terms are not necessary for patentability. Accordingly, Applicants have removed these terms from the independent claims and incorporated them into new dependent claims 43-51. Applicants respectfully traverse the rejection to the extent it may be held to apply to these new claims.

As set forth above, the test for definiteness is whether one skilled in the art would understand the bounds of the claim when read in light of the specification. The instant claims meet this requirement. The specification provides an extensive explanation of analogs and derivatives at page 17, line 1 to page 19, line 10. Therein, Applicants teach that "[e]xendin analogs or derivatives are functional variants having [a] similar amino acid sequence [to] and retaining, to some extent, at least the gastric motility- and gastric emptying-related activities of the related exendin."

A basis for the Examiner's original rejection may stem from the Examiner's apprehension as to the nature of GLP-1, a different peptide, and truncated exendin[9-39], an exendin antagonist, vis a vis the exendins and exendin agonists recited in the independent claims. Applicants respectfully note that the specification clearly establishes that both GLP-1 and truncated exendin[9-39] are not exendins and exendin agonists according to the claimed invention.

Notably, GLP-1 is referred to throughout the specification as being distinct from exendin. This is not surprising given that GLP-1 is understood by those of ordinary skill in the art to be distinct from exendin, including its analogues and derivatives. See, for example, the discussion of exendins and GLP-1 as being in separate groups of peptides on page 2 of EP 1 076 066, a copy of which is attached hereto as **Exhibit A**. GLP-1 is clearly not an exendin derivative because it is not derived from exendin. Rather, GLP-1 has its roots in the human body, while known exendins have their roots in the lizards Heloderma horridum and Heloderma suspectum.

Similarly, GLP-1 is not an exendin analog. One of ordinary skill in the art would not understand GLP-1 to be an exendin analog. For example, no reference cited by the Examiner teaches or suggests that GLP-1 is an "exendin analog." Furthermore, GLP-1 does not have a similar amino acid sequence to that of an exendin. The homology of the amino acid sequence in GLP-1, as compared to the same number of amino acids in an exendin sequence, is only about 53%. When translated over the entire amino acid sequence of an exendin, GLP-1 (a shorter, 30 amino acid peptide) has an even lower homology (approximating 40%). GLP-1 is not an exendin analog according to the present invention.

Similarly, truncated exendin[9-39] is not an exendin agonist, nor is exendin[9-39] an exendin analog or exendin derivative. According to the definition of exendin analogs and exendin derivatives set forth in the specification, exendin[9-39] is not an exendin derivative according to the present invention because it is not a functional variant of the related exendin. In contrast to exendins and exendin agonists, truncated exendin[9-39] was shown to have no effect on gastric emptying. See, for example, Figures 4 and 6 of the specification. Exendin[9-39], in fact, is an exendin antagonist rather than an agonist. Furthermore, truncated exendin[9-39] functions by binding to cloned GLP-1 receptors. See Fehmann, HC, et al., Peptides **15**(3): 453-6, 1994; Thorens, B., et al., Diabetes, **42**(11): 1678-82, 1993, both referred to in the specification. In contrast, the specification teaches that exendins and exendin agonists bind and act on different receptors than cloned GLP-1 receptors with regard to their effects on gastric motility and gastric emptying. See page 23, line 31 to page 24, line 10, and page 33, lines 9-24.

As the specification clearly shows that truncated exendin[9-39] and GLP-1 are not considered exendins or exendin agonists according to the present invention and the definitions of an exendin, exendin analog, and an exendin derivative are clear, Applicants respectfully submit that the claims are definite and clear and ask that the rejection be withdrawn.

4. Derivative Homologies

The Examiner further asserts that Applicants' claims "drawn to methods using exendin derivatives having various percentages of sequence similarity to sequences ... are not defined." Applicants respectfully traverse.

Page 17 of the specification is clear: "Derivatives have at least about 15% sequence similarity." This includes anything above, up to 100%. As discussed, exendins embrace, at a minimum, the structures of exendin-3 and exendin-4, and the percent homologies are thus calculated from these starting points.

Accordingly, as the specification is reasonably clear to one of ordinary skill in the art, Applicants respectfully seek reconsideration and withdrawal of this ground of rejection.

B. The Rejection of Claims 1-11 and 20-30 Under 35 U.S.C. § 112, ¶ 1, Enablement

Claims 1-11 and 20-30 stand rejected under 35 U.S.C. §112, ¶ 1, on the allegation that the specification may not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Although these claims are now cancelled, and new claims introduced, the rejection is traversed.

The Manual of Patent Examining Procedure §2164.04 dictates that the burden initially rests with the Examiner for establishing a reasonable basis to question whether the claimed invention is enabled. To support the rejection, the Examiner can make specific findings of fact, supported by the evidence, and then draw conclusions based on these findings of fact. In any event, specific technical reasons for the Examiner's conclusion are always required in making a rejection for lack of enablement.

The Patent Office has not met the burden of proof required in the instant matter. The Examiner "must provide a reasonable explanation as to why the scope of protection provided by a claim is not adequately enabled by the disclosure." (*See* Manual of Patent Examining Procedure §2164.04, *citing* In re Wright, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)) In this case, the Examiner has not set forth any technical reasons for the conclusions drawn in the Office Action. The Examiner has not even explicitly set forth the scope of the rejected claims, but instead bases grounds for this rejection on asserted uncertainty by what is encompassed by the phrases: gastrointestinal motility, exendin, exendin analog, and exendin derivative. These phrases were discussed above and this new rejection appears to be redundant and misplaced thereover. As these phrases are adequately and clearly supported by the present specification and the Examiner has not provided any specific technical reasons why the claimed invention is not enabled, this rejection should be withdrawn.

Further, to the extent the Examiner discusses physiological mechanism of action, Applicants are not required to know or demonstrate this under the law. *See, e.g., Diamond Rubber Co. v. Consolidated Rubber Tire Co .*, 220 U.S. 428, 435-36 (1911); *Fromson v. Advance Offset Plate, Inc .*, 720 F.2d 1565, 1570, 219 USPQ 1137, 1140 (Fed. Cir. 1983). Applicants have more than demonstrated that exendin and exendin agonists reduce, i.e., lower gastrointestinal motility, a feature that is useful in a variety of contexts, including, e.g., diabetes mellitus, obesity, ingestion of toxins, and diagnostics. Applicants have demonstrated how to evaluate this activity, e.g., using the gastric emptying assays described in Example 1 (page 29). The claimed exploitation of these utilities can be determined by one of ordinary skill in the art without undue experimentation using the guidance provided in the specification.

Accordingly, Applicants respectfully request that the rejection be reconsidered and withdrawn.

C. The Rejection of Claim 25 Under 35 U.S.C. § 112, ¶ 1, Written Description

Claim 25 stands rejected under 35 U.S.C. §112, First Paragraph, as allegedly containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had

possession of the claimed invention. Specifically, the Examiner argues that claim 25 introduces new matter into the specification. This rejection is traversed, but is now moot due to the cancellation of claim 25.[1] Nevertheless, the rejection will be addressed due to the similarity of new claim 45.

The Examiner alleges that "one of skill in the art would not find that Applicant was in possession of the claimed invention at the time the invention was filed." Applicants respectfully disagree.

The Manual of Patent Examining Procedure (MPEP) §2163.05(III) refers to *In re Wertheim*, 541 F.2d 257, 191 USPQ 90 (CCPA 1976) with respect to numerical range limitations in a claim. Specifically, MPEP §2163.05(III) reads in part:

> In the decision in *In re Wertheim*, 541 F.2d 257, 191 USPQ 90 (CCPA 1976), the ranges described in the original specification included a range of "25%-60%" and specific examples of "36%" and "50%." A corresponding new claim limitation to "at least 35%" did not meet the description requirement because the phrase "at least" had no upper limit and caused the claim to read literally on embodiments outside the "25% to 60%" range, however a limitation to "between 35% and 60%" did meet the description requirement.

In the present case, page 17, lines 19-22 teach that derivatives of the invention "have at least about 15% sequence similarity, preferably about 70%, more preferably about 90%, and even more preferably about 95% sequence similarity to the related exendin. Based on the holding in *In re Wertheim*, claim 25, which is directed to "at least about 50% sequence similarity," is well within the range described in the originally filed specification. It is clear that, at the time the application was filed, the inventors had possession of the subject matter set forth in claim 25. Accordingly, claim 25 does not present new matter and this rejection must be withdrawn.

It is also noteworthy that it is well-established that Applicants need not claim all that they are entitled to claim. See, for example, *In re Eickmeyer*, 602 F.2d 974, 981 (CCPA 1979), where the Court held that, in order to "satisfy the description requirement of section 112, first

[1] Claim 25 recited: "The method of claim 1, wherein said exendin derivative has at least

paragraph, an application must contain sufficient disclosure, expressly or inherently, to make it clear to one skilled in the art that the appellant was in possession of the subject matter claimed." The Court then reiterated that one "need not claim all that he is entitled to claim and need have support only for what he does claim." Accordingly, Applicants are entitled to claim an exendin analog or derivative having at least about 50% sequence similarity to the exendin of which it is an analog or derivative, even though Applicants are also entitled to claim at least an exendin analog or derivative having at least about 15% sequence similarity. Again, it is clear that Applicants were in possession of the subject matter of claim 25 at the time the application was filed. This rejection should be withdrawn.

D. The Rejection of Claims 1-3 Under 35 U.S.C. §102(b)

Claims 1-3 remain rejected as allegedly anticipated by Dupre et al. (Dupre, J. et al., Diabetes, **44**, 626-30, 1995) as allegedly evidenced by either Goke et al. (Goke, R. et al., J. Biol. Chem., **268**(26), 19650-55, 1993) or Rai et al. (Rai, A. et al., Am. J. Physiol., **265**: G118-G125, 1993). This rejection is traversed, but is now moot due to the cancellation of claims 1-3 and the Examiner's agreement in the telephonic interview on May 25, 2001.

The Examiner's original argument rested on the assertion that GLP-1[7-36], taught by Dupre et al. to retard gastric emptying of food in normal humans, is an "exendin receptor agonist" according to the presently claimed invention. In making this rejection, the Examiner again alleged that the "specification does not adequately describe the metes and bounds of exendin, exendin derivatives and exendin analogs." As an example, the Examiner stated that "an exendin derivative may be a compound which comprises only 1 amino acid 'derived' from an exendin."

Notwithstanding Applicants' disagreement with this statement, it is noted that the rejections under 35 U.S.C. §112, where the Examiner made the same argument, were discussed above. Again, Applicants respectfully assert that the metes and bounds of exendin, exendin derivatives and exendin analogs are indeed adequately described and taught. As discussed above and agreed to by the Examiner in May 25, 2001 interview, these terms exclude GLP-1.

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about 50% sequence similarity to the exendin of which it is an analog or derivative."

Thus, this rejection must be withdrawn because the cited references do not teach each and every element of Applicants' claimed invention.

E. The Rejection of Claims 1-3 and 6-8 Under 35 U.S.C. § 103(a)

Claims 6-8 remain rejected as allegedly being obvious over Dupre et al. (Dupre, J. et al., Diabetes, **44**, 626-30, 1995) in view of either Chernish et al. (U.S. Patent No. 3,862,301) or Kolterman et al. (PCT Publication No. WO 95/07098) and further in view of Eng (U.S. Patent No. 5,424, 286). The Examiner is now also applying this rejection to claims 1-3. This rejection is traversed, but is now moot due to the cancellation of claims 1-3 and 6-8. Nevertheless, the rejection will still be addressed below for the record.

Similar to the Examiner's 35 U.S.C. §102(b) rejection, the Examiner's argument rests on the assertion that GLP-1[7-36], taught by Dupre et al. to be useful in treating diabetes, is an exendin according to the presently claimed invention. As stated with respect to the 35 U.S.C. §112 Rejections, the Examiner argues that the "specification does not adequately describe the metes and bounds of exendin, exendin derivatives and exendin analogs."

Again, Applicants respectfully assert that the metes and bounds of exendin, exendin derivatives and exendin analogs are indeed adequately described. These terms exclude GLP-1. Agreement on this issue was reached during the interview with the Examiner on May 25, 2001. Thus, this rejection must be withdrawn because the cited references do not teach or suggest each and every element of Applicants' claimed invention.

CONCLUSION

Applicants submit that the pending claims are in condition for allowance, and seek an early notice thereof. Should the Examiner have any remaining questions, the Examiner is encouraged to contact Applicants' undersigned Representative for prompt resolution thereof.

Respectfully submitted,

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Dated: 7/27/01

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MARKED UP COPY OF AMENDED PARAGRAPH IN SPECIFICATION

Compounds particularly useful according to the present invention are exendin agonist compounds of the formula (I):

1 5 10

Xaa_1 Xaa_2 Xaa_3 Gly Thr Xaa_4 Xaa_5 Xaa_6 Xaa_7 Xaa_8

15 20

Ser Lys Gln Xaa_9 Glu Glu Glu Ala Val Arg Leu

25 30

Xaa_{10} Xaa_{11} Xaa_{12} Xaa_{13} Leu Lys Asn Gly Gly Xaa_{14}

35

Ser Ser Gly Ala Xaa_{15} Xaa_{16} Xaa_{17} Xaa_{18} –Z

wherein Xaa_1 is His, Arg or Tyr; Xaa_2 is Ser, Gly, Ala or Thr; Xaa_3 is Asp or Glu [Glu_4]; [Xaa] Xaa_4 is Phe, Tyr or naphthylalanine; Xaa_5 is Thr or Ser; Xaa_6 is Ser or Thr; Xaa_7 is Asp or Glu; Xaa_8 is Leu, Ile, Val, pentylglycine or Met; Xaa_9 is Leu, Ile, pentylglycine, Val or Met; Xaa_{10} is Phe, Tyr or naphthylalanine; Xaa_{11} is Ile, Val, Leu, pentylglycine, tert-butylglycine or Met; Xaa_{12} is Glu or Asp; Xaa_{13} is Trp, Phe, Tyr, or naphthylalanine; Xaa_{14} ,Xaa_{15} , Xaa_{16} and Xaa_{17} are independently Pro, homoproline, 3Hyp, 4Hyp, thioproline, N-alkylglycine, N-alkylpentylglycine or N-alkylalanine; Xaa_{18} is Ser, Thr or Tyr; and Z is –OH or $–NH_2$; with the proviso that the compound does not have the formula of either SEQ. ID. NOS. 1 or 2. Preferred N-alkyl groups for N-alkylglycine, N-alkylpentylglycine and N-alkylalanine include lower alkyl groups preferably of 1 to about 6 carbon atoms, more preferably of 1 to 4 carbon atoms. Suitable compounds include those having amino acid sequences of SEQ. ID. NOS. 5 to 35.